



Post-operative outcomes and predictors of mortality after colorectal cancer surgery in the very elderly patients

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ABSTRACT

Background: The frailty of the very elderly patients who undergo surgery for colorectal cancer negatively influences postoperative mortality. This study aimed to identify risk factors for postoperative mortality in octogenarian and nonagenarian patients who underwent surgical treatment for colorectal cancer.

Methods: This is a single institution retrospective study. The primary outcomes were risk factors for postoperative mortality. The variables of the octogenarians and nonagenarians were compared by using t-test, chi-square test, and Fisher exact test. A multivariate logistic regression analysis was carried out on the combined cohorts.

Results: we identified 319 octogenarians and 43 nonagenarians (N = 362) who underwent surgery for colorectal cancer at the Sant'Orsola-Malpighi university hospital in Bologna between 2011 and 2015. The 30-day postoperative mortality was 6% (N = 18) among octogenarians and 21% (N = 9) for the nonagenarians.

The groups significantly differed in the type of surgery (elective vs. urgent surgery, $p < 0.0001$), ASA score ($p = 0.0003$) and rates of 30-day postoperative mortality (6% vs. 21%, $p = 0.0003$).

In the multivariate analysis ASA > III (OR 2.37, 95% CI [1.43–3.93], $p < 0.001$), and urgent surgery (OR 2.17, 95% CI [1.17–4.04], $p = 0.014$) were associated to post-operative mortality. On the contrary, pre-operative albumin ≥ 3.4 g/dL (OR 0.14, 95% CI [0.05–0.52], $p = 0.001$) was associated with a protective effect on post-operative mortality.

Conclusions: In the very elderly affected by colorectal cancer, preoperative nutritional status and pre-existing comorbidities, rather than age itself, should be considered as selection criteria for surgery. Preoperative improvement of nutritional status and ASA risk assessment may be beneficial for stratification of patients and ultimately for optimizing outcomes.

1. Introduction

Colorectal cancer is the third most common cancer in men and the second in women, with 1,360,000 new cases diagnosed per year worldwide [1]. Surgery is the main curative option in stage I–III and may often prevent cancer-related complications in stage IV. Colorectal cancer most frequently occurs in the elderly: at the time of diagnosis 60% of patients are over the age of 70, and 43% are over 75 [2].

This last point was reinforced by Chouhan et al. who suggested that screening for colorectal cancer in patients over 75 would be justified

where life expectancy warrants it [3].

Foreseeing by the *Global Health and Aging* report, issued by the WHO, predicts that between 2010 and 2050, the world's population of over-85 years old, alias “the oldest old,” will increase by 351% [4]. In this context, it is possible to hypothesize that the amount of oldest old patients needing colorectal cancer surgery in the next future will be remarkably larger than today.

This study aimed to identify risk factors for postoperative mortality in octogenarian and nonagenarian patients who underwent surgical treatment for colorectal cancer. For the oldest old patients undergoing

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colorectal cancer surgery, identification of these factors might lead to more precise risk stratification and optimization of surgical outcomes.

2. Methods

This study was approved in 2016 by the Institutional Review Board (IRB) of St Orsola Malpighi University Hospital and University of Bologna Medical School.

Informed consent was obtained from all patients for accessing their personal data and medical charts for research purposes.

2.1. Inclusion and exclusion criteria

Patients aged 80 years or older with a colorectal cancer diagnosis (ICD-9 CM: 153–154) who consecutively underwent cancer surgery between 2011 and 2015 at the Policlinico Sant'Orsola-Malpighi, in Bologna (362 cases). The sample included elective and urgent surgery (both resections and palliative surgery). We did not apply any particular exclusion criteria since we included all the patients that underwent surgery as reported above.

2.2. Definition and classification of variables

We divided our patients into two categories according to the age: from 80 to 89 years (octogenarians) or ≥ 90 years (nonagenarians).

Length of hospitalization was defined as the number of days from the date of surgical intervention to discharge. The site of the primary tumor was categorized as “right colon,” “transverse colon,” “left colon,” “rectum” or “multiple” (synchronous colorectal tumors). The staging of the tumor was assigned according to the TNM (Tumor Node Metastases) classification of the *American Joint Committee on Cancer/Union for International Cancer Control* [5] and was categorized as $\leq$ III or IV [6]. Pre-operative albumin and hemoglobin were measured by serum levels at the time of admission; all the collected data were categorized with reference to evidence in the literature [7, 8]. We reported the ASA score referring to the classification of the *American Society of Anesthesiologists* [9] while the type of surgical presentation was categorized as “elective” or “urgent.” The surgical operation was classified as “segmental resection of colon,” “right hemicolectomy,” “left hemicolectomy,” “subtotal colectomy,” “sigmoidectomy,” “anterior resection of rectum,” “abdominoperineal resection of rectum” or “other” (palliative surgery). The surgical approach was categorized as “laparotomy,” “laparoscopy,” “laparoscopy converted to laparotomy” or “transanal.” Combined surgery was defined as any surgical procedure which also involved other organs than the colon-rectum (i.e., resection of adjacent organs invaded by cancer, resection of metastases or surgical treatment of any other pathology). Operative time was defined as the time from incision to skin suturing. Complications were defined as events that occurred during hospitalization up to 30 days following the operation. Postoperative mortality was evaluated at 30 and 90 days after the surgery date.

We retrieved the Physiology and Operative Severity Score for enUmeration of Mortality and morbidity (POSSUM) [10], and its latest version Portsmouth POSSUM (P-POSSUM) [11], since these are widely applied in the surgery literature; given the focus of our study we also calculated the colorectal-POSSUM (CR-POSSUM) [12]. We compared the predictive value of POSSUM, P-POSSUM, and CR-POSSUM to assess which of these scores was more accurate in our population. These scores were obtained using the online calculator of the Association of Coloproctology of Great Britain & Ireland [13].

2.3. Statistical analysis

The sample was divided into two cohorts: patients from 80 to 89 (octogenarians) and ≥ 90 (nonagenarians). Variables of the two cohorts were compared using a t-test, chi-square test, and Fisher exact test. A stepwise logistic regression was then carried out on the combined cohorts

(octogenarians and nonagenarians together). Variables with a p-value < 0.10 (age, intensive care admission, pre-operative albumin, surgical program, combined surgery, and ASA score) were selected for multi-variable analysis, where a p-value < 0.05 was considered as the threshold of statistical significance. All statistical analyses were performed with STATA, version n° 13 (*StataCorp 2013. Stata Statistical Software Release 13. College Station, TX: StataCorp LP*).

3. Results

3.1. Characteristics of the patients

Among the octogenarians (N = 319) and nonagenarians (N = 43), ASA score (p = 0.0003), type of surgical presentation (p = 0.0001), 30-day post-operative mortality (p = 0.0003), 90-day post-operative mortality (p = 0.003) were proved to be significantly different.

The 30-day postoperative mortality was 6% (N = 18) among octogenarians and 21% (N = 9) for the nonagenarians, while at 90 days it was respectively 12% (N = 37) and 30% (N = 13).

The octogenarians underwent N = 232 (72.7%) elective procedures: the postoperative mortality was 3.5% (N = 8) at 30 days and 7.6% (N = 18) at 90 days. The nonagenarians underwent N = 18 (41.9%) elective procedures: the postoperative mortality was 11.1% (N = 2) at 30 days and 16.7% (N = 3) at 90 days.

The cohort of nonagenarians had a worse ASA score, a higher percentage of urgent surgical interventions (53%) and a higher rate of mortality at 30 (21%) and 90 days postoperatively (30%). The octogenarian group had a larger number of elective surgeries (86%). Among octogenarians and nonagenarians, there were no significant differences regarding sex, length of hospitalization (LOS) and intensive care admission rates. No significant differences were found regarding the site of the primary tumor, tumor stage, pre-operative albumin, hemoglobin levels, type of operation, surgical approach, operative time and rates of post-operative complications. The following tables show a comparison of the variables in detail (Tables 1, 2, 3, and 4).

3.2. Factors associated to 30-day postoperative mortality

In the combined cohort, urgent surgery (OR 2.17, 95% CI [1.17–4.04], p = 0.014) and ASA score $>$ III (OR 2.37, 95% CI [1.43–3.93], p < 0.001) were significantly associated to postoperative mortality. On the contrary, pre-operative albumin ≥ 3.4 g/dL (OR 0.14, 95% CI [0.05–0.52], p = 0.001) was associated with a protective effect on postoperative mortality.

Age ≥ 90 (OR 1.21, 95% CI [0.31–4.68], p = 0.77), Intensive Care admission (OR 1.18, 95% CI [0.65–2.13], p = 0.58) and combined surgery (OR 1.03, 95% CI [0.19–5.01], p = 0.87) did not represent significant risk factors for postoperative mortality (Table 5).

Table 1
Demographics and clinical data.

Variable	Octogenarians (N = 319)	Nonagenarians (N = 43)	p-value
Age (years)	83.6 $\pm$ 2.7	91.9 $\pm$ 2.2	0.653
Sex			0.212
F	169 (53%)	27 (63%)	
M	150 (47%)	16 (37%)	
ASA Score			0.0003
II	19 (6%)	0 (0%)	
III	253 (79%)	25 (58%)	
IV	47 (15%)	18 (42%)	
Surgical presentation			<0.0001
Urgent	44 (14%)	23 (53%)	
Elective	275 (86%)	20 (47%)	
Intensive Care admission	186 (58%)	26 (62%)	0.753

Data is reported as number (Percentage) or Mean $\pm$ Standard Deviation.

Table 2
Pathology and laboratory data.

Variable	Octogenarians (N = 319)	Nonagenarians (N = 43)	p-value
Site of primary tumor			
Right colon	137 (43%)	22 (52%)	0.192
Transverse colon	31 (10%)	5 (11%)	
Left colon	76 (24%)	14 (32%)	
Rectum	65 (20%)	2 (5%)	
Multiple	10 (3%)	0 (0%)	
Stage			
0	12 (4%)	0 (0%)	0.091
I	49 (15%)	3 (6%)	
II	139 (44%)	26 (60%)	
III	103 (32%)	13 (31%)	
IV	16 (5%)	1 (3%)	
Pre-operative albumin (g/dL)	3.9 ± 1.5	3.6 ± 1.3	0.544
Pre-operative haemoglobin (g/dL)	11.4 ± 2.1	11.7 ± 2.4	0.886

Data is reported as number (Percentage) or Mean ± Standard Deviation.

3.3. Expected, observed mortality and morbidity overall and by type of surgery and by age

Overall expected mortality by type of surgery followed the order P-POSSUM < CR-POSSUM ($p < 0.0001$) (Table 6). This statistical significance held when comparing elective and emergent procedures in the same order. In fact, all scores were higher in the emergent surgery group ($p < 0.0001$). The expected morbidity (POSSUM score) was significantly different when comparing elective and emergent cases ($p < 0.0001$). For observed morbidity, a higher number of complications was found in the elective surgery group (28.21%) compared to the emergent surgery group (17.11%) but was not statistically significant ($p = 0.025$).

Overall expected mortality by age followed the order P-POSSUM < CR-POSSUM ($p = 0.013$ and 0.001 respectively) (Table 7). For observed mortality, the comparison between the octogenarians and nonagenarians group was statistically significant (6% versus 21%, $p = 0.0003$).

The comparison of the expected morbidity (POSSUM) between the age groups was statistically significant (<0.0001). With respect to the observed morbidity in octogenarians and nonagenarians population, the comparison did not reach statistical significance.

4. Discussion

The possibility of operating on the oldest old for colorectal cancer has

Table 3
Operative features.

Variable	Octogenarians (N = 319)	Nonagenarians (N = 43)	p-value
<i>Surgical procedure</i>			
Subtotal colectomy	16 (5%)	2 (5%)	0.783
Right hemicolectomy	149 (47%)	24 (57%)	
Left hemicolectomy	45 (14%)	2 (5%)	
Abdominal-perineal resection of rectum	10 (3%)	1 (2%)	
Anterior resection of rectum	45 (14%)	3 (6%)	
Segmental resection	15 (5%)	3 (6%)	0.681
Sigmoidectomy	21 (7%)	6 (14%)	
Other	18 (6%)	2 (5%)	
<i>Surgical approach</i>			
Laparotomy	271 (85%)	35 (81%)	0.061
Laparoscopy	35 (11%)	6 (15%)	
Laparoscopy converted to laparotomy	9 (3%)	1 (2%)	
Transanal	4 (1%)	1 (2%)	
Combined surgery	70 (22%)	4 (9%)	
Operative time (min)	252 ± 33	223 ± 51	0.209

Data is reported as number (Percentage) or Mean ± Standard Deviation.

Table 4
Outcomes.

Variable	Octogenarians (N = 319)	Nonagenarians (N = 43)	p-value
Length of stay (days)	14.2 ± 12.5	11.4 ± 7.4	0.287
Post-operative complications			
- Surgical			0.974
Major			
Gastrointestinal haemorrhage	5 (2%)	1 (1%)	
Dehiscence of anastomosis	6 (2%)	0 (0%)	
Intestinal occlusion	3 (1%)	0 (0%)	
Minor			0.0003
Hematoma of the wound	8 (3%)	1 (1%)	
Infection of the wound	12 (4%)	3 (1%)	
Dehiscence of the wound	4 (1%)	0 (0%)	
- Clinical			
Myocardial infarction	4 (1%)	1 (1%)	
Pneumonia	9 (3%)	1 (1%)	
Cerebral or vascular event	4 (1%)	1 (1%)	
Multi-organ failure	5 (2%)	1 (1%)	
Urinary tract infections	5 (2%)	1 (1%)	
2 or more clinical complications	15 (5%)	0 (0%)	
30-day post-operative mortality	18 (6%)	9 (21%)	0.0003
90-day post-operative mortality	37 (12%)	13 (30%)	0.003

Data is reported as number (Percentage) or Mean ± Standard Deviation.

been discussed in the past. Many studies showed the feasibility of performing colorectal surgery in the oldest old, in particular demonstrating the benefits of laparoscopy which sometimes is not offered as a surgical approach given multiple cardiopulmonary comorbidities and the related difficulties with tolerating the pneumoperitoneum [14, 15].

In the present study, 86% of the octogenarians underwent elective surgery. It appears likely that in most cases the clinical presentation of the disease allowed planning an elective procedure.

On the other hand, 53% of the nonagenarians were operated following an urgent surgical presentation. In the study by Arenal and colleagues, the patients over-90 years with colorectal cancer who underwent urgent surgery accounted for 49% of the sample [16]. These data are similar to other reports [17, 18, 19, 20]. The possible explanation for this recurrent urgent presentation in nonagenarian patients is that the diagnosis was frequently triggered by a complication manifestation. With respect to this fact, it is worth mentioning that among the nonagenarians of our report, 40% of the cases had an ASA score > III. ASA scores differed significantly between octogenarians and nonagenarians patients. Most likely, the nonagenarians, as opposed to the octogenarians, arrived at the pre-operative visit with a worse functional deficit and more serious comorbidities.

In the cohort of octogenarians, 30-day postoperative mortality occurred in 6% of cases. Our observation is comparable with the post-operative (within 30 days) mortality data of elderly patients undergoing colorectal cancer surgery. In fact, Verweij and colleagues reported that the rate of postoperative mortality of over-85 patients who underwent surgical treatment for colorectal cancer was 10% [21]. In addition, Damhuis and colleagues found that postoperative mortality after colorectal cancer surgery was 8% in the age group 80–84 and 13% in the age group 85–89²².

On the contrary, if we take into consideration our cohort of nonagenarian patients, 30-day postoperative mortality was 21%. This observation also seems to be in line with the current literature on the topic. In the study by Arenal, postoperative mortality of over-90 patients undergoing colorectal cancer surgery was 25% [16] while in the study by Damhuis it

Table 5

Multivariate analysis of the factors associated to 30-day post-operative mortality.

Variable	Odd Ratios	95% Confidence interval	p-value
<i>Age</i>			
Octogenarians	-	-	0.775
Nonagenarians	1.21	0.31–4.68	
<i>Intensive Care admission</i>			
Yes	1.18	0.65–2.13	0.583
No	-	-	
<i>Pre-operative albumin (g/dL)</i>			
>3,4	0.14	0.05–0.52	0.001
≤3,4	-	-	
<i>Type of surgical presentation</i>			
Elective	-	-	0.014
Urgency	2.17	1.17–4.04	
<i>ASA Score</i>			
≤ III	-	-	<0.001
> III	2.37	1.43–3.93	
<i>Combined surgery</i>			
Yes	1.03	0.19–5.01	0.87
No	-	-	

was 20% [22]. In our report, the rate of both 30-day and 90-day post-operative mortality in nonagenarians was significantly higher than in octogenarians (Table 4). The multivariate analysis of the combined cohort indicated, however, that age ≥ 90 did not correlate with mortality; on the contrary, urgent surgical presentation and an ASA score $> III$ were associated with postoperative mortality.

Therefore, we hypothesize that the significant difference in post-operative mortality between octogenarians and nonagenarians could be due, not so much to the average group age, but to the fact that nonagenarians presented more frequently in urgency and with a higher ASA with respect to the octogenarians. Our hypothesis is supported in literature by Biondi et al. who demonstrated that age itself should not be considered as a risk factor for the development of complications in patients undergoing surgery for colorectal cancer [23].

Several studies have been investigating POSSUM, P-POSSUM, and CR-POSSUM prediction of mortality and morbidity in elderly patients [24, 25, 26, 27, 28]. The heterogeneity of these data should prompt to assess these scores in different populations, settings, and geographic locations, since other variables may influence morbidity and mortality, especially in the elderly. The fact that P-POSSUM involves cardiorespiratory variables that are not measurable objectively may contribute to this variability.

4.1. Factors associated with postoperative mortality in the combined cohort

In the combined cohort, ASA $> III$, pre-operative albumin < 3.4 g/dL, and urgent surgery were associated with postoperative mortality. In literature, there is wide consensus on the causal relation “ASA – post-

Table 6

Expected, observed mortality and morbidity overall and by elective or emergent surgery.

Score	Overall	Elective (N = 251)	Emergent (N = 111)	p value
<i>Expected mortality, %</i>				
CR-POSSUM	33.60 $\pm$ 11.36	30.47 $\pm$ 7.04	42.64 $\pm$ 15.81	<0.0001
P-POSSUM	8.31 $\pm$ 8.25	6.39 $\pm$ 4.67	12.45 $\pm$ 11.97	<0.0001
Observed mortality No.(%)	27 (7.45%)	8 (3.18%)	19 (17.11%)	<0.0001
<i>Expected morbidity, %</i>				
POSSUM	65.44 $\pm$ 9.98	61.49 $\pm$ 8.74	73.93 $\pm$ 6.61	<0.0001
Observed morbidity No.(%)	90 (24.86%)	71 (28.21%)	19 (17.11%)	0.025

operative mortality” for elderly patients who have undergone colorectal cancer surgery [29, 30, 31]. In a study of patients over 80 years old undergoing colorectal cancer surgery, the risk of postoperative mortality, in the presence of ASA $> III$, was six times higher than the control group (65–80 years old) [32]. More recently, a study by Soler et al. showed that ASA in patients over 75 years old was a direct predictor of anastomotic leaks as well as strictly medical postoperative complications [5, 33]. According to our experience, in the oldest old, the higher ASA score may correlate to lower functional reserves and more significant comorbidities, enough to influence short-term outcomes.

For the oldest old patients with colorectal cancer, pre-operative albumin levels have already been correlated to surgical outcomes in literature [29, 34]. The serum albumin concentration may be considered an indicator of the patient's nutritional status [29].

The correlation between urgent surgical presentation and operative mortality, for the oldest old undergoing colorectal cancer surgery, is confirmed in the studies previously referenced [2, 30, 32]. In fact, an urgent surgical presentation in an old patient may frequently point at a diagnosis of bowel obstruction or perforation. These two diagnoses carry a poor prognosis independently from the surgical operation; it is possible that the physical and mental stress related to the surgery along with the general anesthesia's effects further worsen short-term outcomes in such frail conditions.

4.2. Perspectives

According to several observations, important predictors of post-operative mortality in the oldest old patients who have undergone surgery for colorectal cancer are ASA score and urgent surgical presentation [17, 35, 36]. Age did not represent a factor associated with postoperative mortality in previous reports [37, 38]. Our analysis points to serum albumin concentration < 3.4 g/dL (i.e., malnutrition) as a further parameter positively correlated to postoperative mortality. Considering these results, it appears appropriate planning prospective studies in order to achieve even stronger evidence regarding the safety of the oldest old undergoing colorectal cancer surgery. Age did not represent an independent risk factor for postoperative mortality; patients should be assessed according to their general physical condition, whatever the age.

In several studies similar to our own, ASA score and albumin serum concentration are reported as indirect indicators of the patient's functional conditions [20, 27, 39]. In recent research, multidimensional geriatric assessment has shown to be useful in giving a 360° picture of a patient's status, in terms of physical and functional condition [40, 41]. Thus, the combination of geriatric assessment and consolidated prognostic indicators, such as the TNM staging, could lead to more effective algorithms for preoperative risk stratification. We believe further studies should focus on confirming the clinical usefulness of functional variables (e.g. ASA score and albumin concentration) as postoperative mortality

Table 7

Expected, observed mortality and morbidity overall and by age.

Score	Overall	Octogenarians (N = 319)	Nonagenarians (N = 43)	p value
<i>Expected mortality, %</i>				
CR-POSSUM	33.60 $\pm$ 11.36	32.28 $\pm$ 9.18	42.71 $\pm$ 18.66	0.001
P-POSSUM	8.31 $\pm$ 8.25	7.79 $\pm$ 7.75	12.07 $\pm$ 10.51	0.013
Observed mortality No.(%)	27 (7.45%)	18 (6%)	9 (21%)	0.0003
<i>Expected morbidity, %</i>				
POSSUM	65.44 $\pm$ 9.98	64.46 $\pm$ 9.34	72.39 $\pm$ 11.60	<0.0001
Observed morbidity No.(%)	90 (24.86%)	80 (25%)	10 (23.25%)	0.71

predictors. Keeping in mind what mentioned above, a clinical intervention, aiming to modify the individual's nutritional and functional aspects, might improve short-term outcomes. However, since most of the surgeries on nonagenarians are performed in an emergent status, significant results for nutritional interventions might be difficult to achieve before surgery.

4.3. Limitations

This study has the limitations of retrospective investigations involving chart review. In addition, given the rarity of an operation on a nonagenarian, the sample's size might limit the statistical power and the generalization of the conclusions. It is hard to generalize the conclusions also considering that this is a single study institution. A further limitation of our report was the lack of a standardized institutional protocol for postoperative care. Moreover, using albumin as a marker of nutrition is suboptimal and may be inaccurate under certain conditions. Preoperative pre-albumin should be ideally collected in further studies to have a more accurate description of the patients' nutrition status.

5. Conclusions

From the current analysis of a large database of 362 octogenarians and nonagenarians patients who have undergone colorectal cancer surgery, serum albumin < 3.4 g/dL, urgent surgical presentation, and ASA score > III, but not age ≥ 90, were correlated to postoperative mortality.

These results should prompt an improvement in multidimensional geriatric assessment, to better define the risk stratification in the oldest old patients undergoing colorectal surgery. Additionally, the development of effective corrective interventions of the above preoperative functional variables might lead to an improvement of surgical outcomes in the increasingly large geriatric population.

Declarations

Author contribution statement

Matteo Novello, Francesco Vito Mandarinò: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Salomone Di Saverio: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Davide Gori: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Marialuisa Lugaesi, Giuseppe Cavallari: Contributed reagents, materials, analysis tools or data.

Alessandro Duchi, Francesca Argento: Performed the experiment; Contributed reagents, materials, analysis tools or data.

James Wheeler: Analyzed and interpreted the data; Wrote the paper.

Bruno Nardo: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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